Eur. J. Med. Chem. 36 (2001) 469–479

PII: S0223-5234(01)01240-5/FLA

Short communication

Synthesis and cytotoxicity of artemisinin derivatives containing cyanoarylmethyl group

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Received 18 January 2001; revised 23 April 2001; accepted 2 May 2001

Abstract – A series of 12α-deoxoartemisinyl cyanoarylmethyl dicarboxylates (**4a**–**4o**), dicarboxylic acids 12α-deoxoartemisinyl ester cyanoarylmethyl amide (**5a**–**5k**), and dicarboxylic acids 12α-deoxoartemisinyl ester *N*-methylcyanoarylmethyl amide (**6a**–**6l**), showing moderate cytotoxicity against P388 and L1210 cells were prepared. They induced the significant accumulation of L1210 and P388 cells in the G1 phase of the cell cycle. This mechanism of action was quite different from that of the majority of cytotoxic compounds used in the chemotherapy of cancer. Compound **4b** possessed better cytotoxicity than the other compounds. © 2001 Éditions scientifiques et médicales Elsevier SAS

artemisinin derivatives / cyanoarylmethyl group / cytotoxicity

1. Introduction

Artemisinin (**1a**) and its derivatives (dihydroartemisinin (**1b**), artemether (**1c**), arteether (**1d**), and artesunate (**3a**)) distinguished themselves as a new generation of antimalarial drugs with low toxicity [1]. Some of them possess other bioactivities also [2]. In our laboratory it was found that the new type of artemisinin derivatives, cyano-4′-bromophenylmethyl 12β-deoxoartemisinyl ether (**2a**) was notably active in vitro against P388 and A549 cell lines and block the cell cycle progression of P388 murine leukemia cells in the G1 phase [3]. Recently it was also reported that artesunate showed antitumor activity both in vitro and in vivo [4]. Based on these facts, a combination of α-hydroxyarylacetonitrile with artesunate and by changing of some the substituents might lead to yet another new type of antitumor agent. Thus, 12α-deoxoartemisinyl cyanoarylmethyl dicarboxylates (**4a**–**4o**) dicarboxylic acid 12α-deoxoartemisinyl ester cyanoarylmethyl amide (**5a**–**5k**) and *N*-methylcyanoarylmethyl amide (**6a**–**6l**) were prepared. Some of the new artemisinin derivatives showed moderate cytotoxicity in vitro against L1210 and P388 cell lines having a mechanism of action similar to compound **2a**. Compound **4b** was the best one in the series next to compound **2a** (*figure 1*).

2. Chemistry

Artemisinin (**1a**) was reduced by sodium borohydride to give dihydroartemisinin (**1b**), which reacted with succinic anhydride to yield artesunate (**3a**) according to literature procedure [5, 6]. Other dicarboxylic acids mono-12α-deoxoartemisinyl ester

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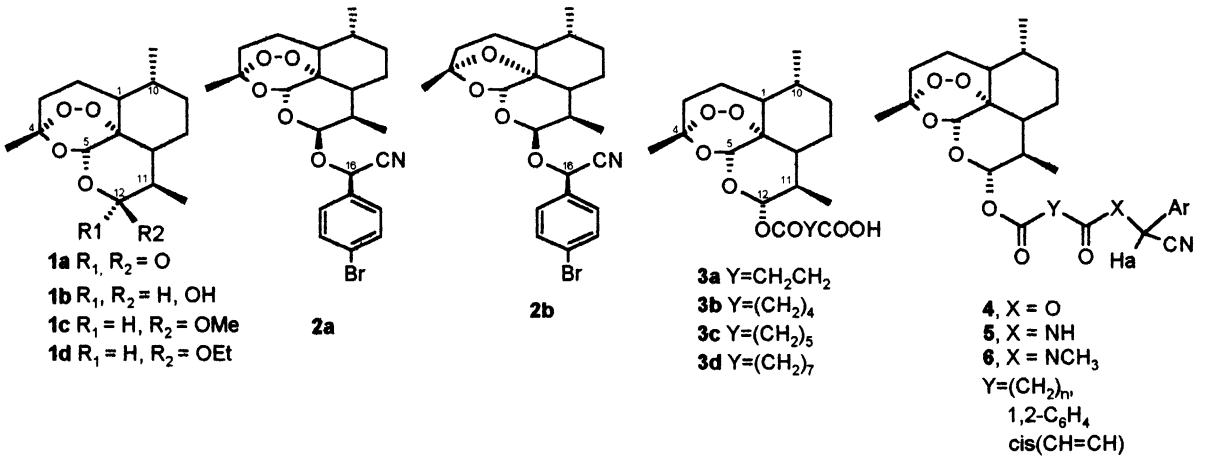

Figure 1. Structures of compounds **1**–**6**.

(**3b**–**3d**) was prepared by the condensation of dicarboxylic acid with dihydroartemisinin in the presence of DCC and DMAP (*figure 2*). α-Hydroxyarylacetonitrile and α-aminoarylacetonitrile were obtained from aromatic aldehyde by following the procedure outlined in Refs. [7–9]. If ammonia solution was replaced by methylamine solution during the preparation of α-aminoarylacetonitrile, then *N*-methyl-α-aminoarylacetonitrile was obtained. The esters (**4a**–**4o**) were prepared by the condensation of dicarboxylic acid mono-12α-deoxoartemisinyl ester (**3a**–**3d**) with α-hydroxyarylacetonitrile in the presence of DCC and DMAP. Similarly, the amides (**5a**–**5k**) were produced from artesunate (**3a**) and α-aminoarylacetonitrile (*figure 3*). The amides (**6a**–**6l**) were prepared by the condensation of **1b** with dicarboxylic acid mono-*N*-methyl-cyanoarylmethyl amide (**7a**–**7l**) prepared by the reaction of dicarboxylic anhydride and *N*-methyl-α-aminoarylacetonitrile in the presence of triethylamine (*figure 4*).

These esters and amides were purified using column chromatography and some of them were recrystallized from ethyl acetate–petroleum ether. However, others exist as amorphous solid. All the products tested were 12α-isomers as indicated by the large coupling constants (J>9 Hz) between 11-H and 12-H in ^{1}H NMR (the β-isomers, $J \approx 3$–4 Hz). As α-hydroxyarylacetonitrile, α-aminoarylacetonitrile or *N*-methyl-α-aminoarylacetonitrile possess a chiral center, all esters and amides (**4**–**6**) possess a pair of epimer that could not be discriminated on TLC and were hence separated using column chromatography (*table I*).

3. Pharmacology

3.1. Cell culture and cytotoxity

The murine L1210 and P388 leukemia and human lung A549 carcinoma cell lines were cultivated in RPMI 1640 medium supplemented with 10% fetal calf serum, 2

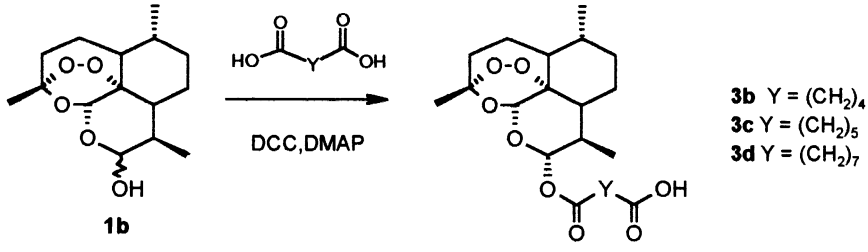

Figure 2. Synthesis of compound **3**.

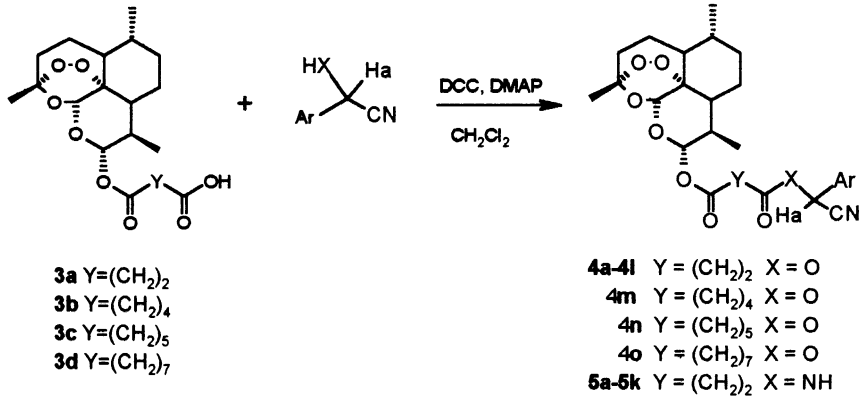

Figure 3. Synthesis of compounds **4** and **5**.

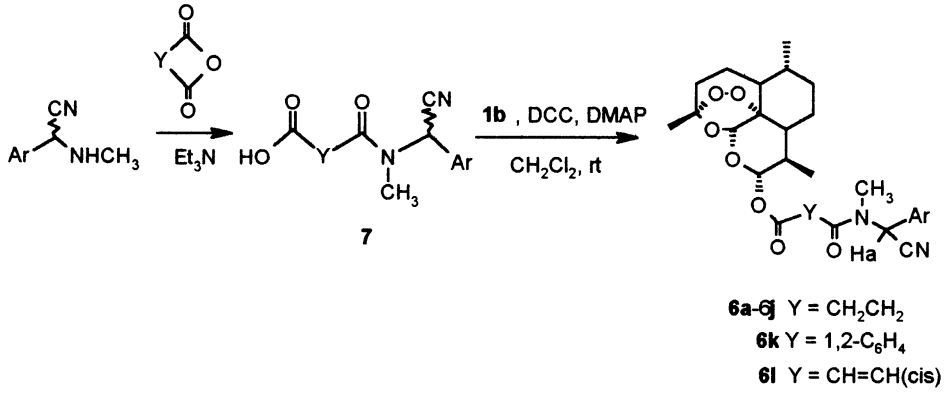

Figure 4. Synthesis of compound **6**.

mM L-glutamine, 100 units mL^{-1} penicillin, 100 μg mL^{-1} streptomycin, and 10 mM HEPES buffer (pH 7.4). The in vitro cytotoxicity of these artemisinin derivatives to the murine and human cancer cells was defined by the microculture tetrazolium assay as described in Ref. [10]. Briefly, L1210, P388 and A549 cells were exposed to graded concentrations of the drug for 48 and 96 h, respectively (4 doubling times). Results were expressed as IC_{50}, the concentration that reduced by 50% the optical density of the treated cells with respect to the density of untreated cells. Vincristine Sulfate (VCR) was used as a reference cytotoxic compound.

3.2. Cell cycle and apoptosis

L1210 and P388 cells (2.5×10^5 mL^{-1}) were first incubated for 21 h in various concentrations of the drugs followed by cells being fixed in 70% ethanol and incubated for 30 min in PBS containing 100 μg mL^{-1} RNAse and 50 μg mL^{-1} propidium iodide (PI, Sigma). For each sample, 10^4 cells were analyzed on an Epics XL/MCL flow cytometer (Becgman counter, France). Results are expressed as the percentage of cells in the G_1 phase of the cell cycle and in the sub-G_1 phase (apoptotic cells). Apoptotic cells were also quantified by flow cytometry using the annexin-V-FITC labeling. The results are shown in *table II*.

4. Results and discussion

The cytotoxicity of these artemisinin derivatives are listed in *table II*.

The data in *table II* indicated that some of these compounds had moderate cytotoxicity to L1210 and P388 but less cytotoxicity to A549. Some of these compounds **4**–**6** as well as compound **2a** could block

the cell cycle progression of P388 murine leukemia cells in the G_1 phase and induced apoptose. Some compounds also acted on the L1210 cells in the same mode. Of the compounds examined, the ester **4** showed potent cytotoxicity against L1210 and P388 cells; compound **4b** was the best one; and the amide **6** appeared to be better than amide **5** against P388 cells. We found that a deoxoartemisinyl moiety was required. As **2a** showed good cytotoxity against P388 and A549, its deoxy analog **2b** was inactive [3]. Compounds **4b** and **4m**, **4a** and **4n**, **4d** and **4o** having the same aryl moiety, respectively, in spite of chain length ($Y = C_2$–C_7), showed a similar cytotoxicity. Similar results were also observed in the case of amides **6j**, **6k** and **6l**. Moreover, the electronegativity and the bulk of the substituent that attach to the aryl ring play an insignificant role in cytotoxicity. Therefore, the relationship between cytotoxicity and chemical structure was not so clear. In other words, compounds **4**–**6** derived from the insertion of dicarboxylic acid radical between the cyanoarylmethyl and deoxoartemisinyl groups showed less cytotoxicity than that of compound **2a**.

Table I. Physico-chemical data of compounds **4**–**6**.

Compound	Ar	Y	X	M.p. (dec.) (°C)	Yield (%)	Molecular formula
4a	C_6H_5	$(CH_2)_2$	O	142–144	31	$C_{27}H_{33}NO_8$
4b	2-ClC_6H_4	$(CH_2)_2$	O	amorphous	37	$C_{27}H_{32}ClNO_8$
4c	4-ClC_6H_4	$(CH_2)_2$	O	amorphous	27	$C_{27}H_{32}ClNO_8$
4d	2-BrC_6H_4	$(CH_2)_2$	O	amorphous	83	$C_{27}H_{32}BrNO_8$
4e	4-BrC_6H_4	$(CH_2)_2$	O	amorphous	60	$C_{27}H_{32}BrNO_8$
4f	4-CNC_6H_4	$(CH_2)_2$	O	amorphous	57	$C_{28}H_{32}N_2O_8$
4g	4-$NO_2C_6H_4$	$(CH_2)_2$	O	amorphous	25	$C_{27}H_{32}N_2O_{10}$
4h	4-$OMeC_6H_4$	$(CH_2)_2$	O	amorphous	42	$C_{28}H_{35}NO_9$
4I	2,4-$(OMe)_2C_6H_3$	$(CH_2)_2$	O	amorphous	40	$C_{29}H_{37}NO_{10}$
4j	3,4-$(OMe)_2C_6H_3$	$(CH_2)_2$	O	amorphous	60	$C_{29}H_{37}NO_{10}$
4k	3-OMe, 4-Obz C_6H_3	$(CH_2)_2$	O	amorphous	79	$C_{35}H_{41}NO_{10}$
4l	3,4-$OCH_2OC_6H_3$	$(CH_2)_2$	O	amorphous	68	$C_{28}H_{33}NO_{10}$
4m	2-ClC_6H_4	$(CH_2)_4$	O	amorphous	65	$C_{29}H_{36}ClNO_8$
4n	C_6H_5	$(CH_2)_5$	O	amorphous	60	$C_{31}H_{41}NO_8$
4o	2-BrC_6H_4	$(CH_2)_7$	O	amorphous	42	$C_{32}H_{42}BrNO_8$
5a	C_6H_5	$(CH_2)_2$	NH	153–154	24	$C_{27}H_{34}N_2O_7$
5b	2-FC_6H_4	$(CH_2)_2$	NH	161–162	40	$C_{27}H_{33}FN_2O_7$
5c	3-FC_6H_4	$(CH_2)_2$	NH	146–148	28	$C_{27}H_{33}FN_2O_7$
5d	4-FC_6H_4	$(CH_2)_2$	NH	158–160	37	$C_{27}H_{33}FN_2O_7$
5e	3-ClC_6H_4	$(CH_2)_2$	NH	154–156	24	$C_{27}H_{33}ClN_2O_7$
5f	4-ClC_6H_4	$(CH_2)_2$	NH	164–165	22	$C_{27}H_{33}ClN_2O_7$
5g	2-BrC_6H_4	$(CH_2)_2$	NH	156–159	24	$C_{27}H_{33}BrN_2O_7$
5h	3-BrC_6H_4	$(CH_2)_2$	NH	153–156	38	$C_{27}H_{33}BrN_2O_7$
5I	4-BrC_6H_4	$(CH_2)_2$	NH	165–167	30	$C_{27}H_{33}BrN_2O_7$
5j	4-$NMe_2C_6H_4$	$(CH_2)_2$	NH	160–162	32	$C_{29}H_{39}N_3O_7$
5k	2-naphthyl	$(CH_2)_2$	NH	amorphous	49	$C_{31}H_{36}N_2O_7$
6a	C_6H_5	$(CH_2)_2$	NMe	amorphous	47	$C_{28}H_{36}N_2O_7$
6b	2-FC_6H_4	$(CH_2)_2$	NMe	amorphous	59	$C_{28}H_{35}FN_2O_7$
6c	3-FC_6H_4	$(CH_2)_2$	NMe	amorphous	56	$C_{28}H_{35}FN_2O_7$
6d	4-FC_6H_4	$(CH_2)_2$	NMe	amorphous	81	$C_{28}H_{35}FN_2O_7$
6e	2-ClC_6H_4	$(CH_2)_2$	NMe	amorphous	48	$C_{28}H_{35}ClN_2O_7$
6f	4-ClC_6H_4	$(CH_2)_2$	NMe	amorphous	70	$C_{28}H_{35}ClN_2O_7$
6g	2-BrC_6H_4	$(CH_2)_2$	NMe	amorphous	33	$C_{28}H_{35}BrN_2O_7$
6h	4-BrC_6H_4	$(CH_2)_2$	NMe	amorphous	80	$C_{28}H_{35}BrN_2O_7$
6I	2,4-$Me_2C_6H_3$	$(CH_2)_2$	NMe	amorphous	43	$C_{30}H_{40}N_2O_7$
6j	3 (3-$CF_3C_6H_4$)OC_6H_4	$(CH_2)_2$	NMe	amorphous	53	$C_{35}H_{39}F_3N_2O_8$
6k	C_6H_5	1,2-C_6H_4	NMe	amorphous	70	$C_{32}H_{36}N_2O_7$
6l	C_6H_5	CH=CH (*cis*)	NMe	amorphous	45	$C_{28}H_{34}N_2O_7$

Table II. Cytotoxicity of compounds **4–6**.

No.	IC_{50} (nM)			Cell cycle effect L1210% G_1 (nM)	Cell cycle apoptosis P388		
	L1210	A549	P388		% G_1	% Apoptose	nM
VCR	4.8	12.4	1.81				
2a		39	11		63	51	25
2b		41 990	24 200				
4a	120	2400	178		63	48	500
4b	38	845	57		72	54	200
4c	89	>50 μM	370	60(400)	65	51	500
4d	141	497	418	71(400)	58	44	500
4e	396		406	64(1000)			
4f	101	7130	360	61(400)	60	41	500
4g	109	>25 μM	517	60(600)	60	38	500
4h	88	6320	414	59(600)	68	50	500
4I	87	7135	373	67(400)	65	42	500
4j	107	8260	474	60(400)	58	33	500
4k	68	4864	324	67(400)	59	50	500
4l	92	>50 μM	446	63(400)	58	33	500
4m	79		401	59(500)	32	44	500
4n	197	4633	265		62	48	500
4o	50		258	57(400)	65	41	500
5a		4700	500		75	31	1000
5b		4300	500		77	32	1000
5c		4700	600		76	41	1000
5d		4600	700		76	39	2500
5e		3000	500		77	42	1000
5f		4300	600		76	41	1000
5g		4600	600		76	40	1000
5h		4800	1100		75	41	1000
5i		4200	600		75	38	1000
5j		4400	600		76	30	1000
5k		5300	700		77	34	1000
6a	369	12 842	395	64(1000)			
6b		13 970	297		70	29	2000
6c		13 400	259		69	36	2000
6d	352			64(500)			
6e		6100	300		76	24	1000
6f	375	7343	260	64(1000)			
6g		16 100	364		69	30	2000
6h	370	5300	210	66(1000)			
6i		7660	195		69	27	1000
6j		2500	300		77	34	500
6k	450	10 900	320	66(1000)			
6l		19 200	434		70	27	2500

5. Experimental

5.1. Chemistry

All melting points (m.p.) were calculated in open capillary using a BUCHI-510 melting point apparatus and were uncorrected. The IR spectra were run on a Perkin–Elmer 599B spectrophotometer. ^{1}H NMR spectra were determined in $CDCl_3$ solution on a NMR Brucker AM-400. Elemental analyses were performed by elementary vario EL and all the results were within 0.4% of the theoretical values. All the reagents used were commercially available.

5.1.1. General procedure

*5.1.1.1. Preparation of compounds **3***

DCC (1.13 g, 5.5 mmol) and DMAP (30 mg) were added to a solution of dihydroartemisinin (1.42 g, 5

mmol) and dicarboxylic acid (6 mmol) in 30 mL CH_2Cl_2. The mixture was stirred at room temperature (r.t.) until the reaction was completed. After the insoluble DCCU was filtered off, the solvent was moved and the residue was purified using column chromatography (5:1 petroleum ether–ethyl acetate) to give **3**. Yield: 45–55%.

5.1.1.2. Adipic acid mono-12α-deoxoartemisinyl ester ***(3b)***

Yield: 50%. ^{1}H NMR ($CDCl_3$, δ ppm): 5.77 (d, 1H, 12-H, [$J = 9.79$ Hz]); 5.47 (s, 1H, 5-H,); 2.34 (m, 4H, –$COCH_2$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.70$ Hz]), 0.82 (3H, d, 10-CH_3, [$J = 7.14$ Hz]).

5.1.1.3. Pimelic acid mono-12α-deoxoartemisinyl ester ***(3c)***

Yield: 55%. ^{1}H NMR ($CDCl_3$, δ ppm): 5.75 (d, 1H, 12-H, [$J = 9.80$ Hz]); 5.45 (s, 1H, 5-H); 2.40 (m, 4H, –$COCH_2$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.71$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.11$ Hz]).

5.1.1.4. Azelaic acid mono-12α-deoxoartemisinyl ester ***(3d)***

Yield: 45%. ^{1}H NMR ($CDCl_3$, δ ppm): 5.77 (d, 1H, 12-H, [$J = 9.79$ Hz]); 5.44 (s, 1H, 5-H); 2.40 (m, 4H, –$COCH_2$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.74$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.12$ Hz]).

5.1.1.5. Preparation of compounds ***4*** *and* ***5***

DCC (2.26 g, 11 mmol) and DMAP (50 mg) were added to a solution of dicarboxylic acid monodeoxoartemisinyl ester (**3**) (10 mmol) and α-hydroxyarylacetonitrile (or α-aminoarylacetonitrile) (l2 mmol) in 50 mL CH_2Cl_2. The solution was stirred at r.t. for 4 h. After filtrating the DCCU, the solvent was removed and the residue was purified by column chromatography (10:1 petroleum ether–ethyl acetate) to give compounds **4** or **5**.

5.1.1.6. 12α-Deoxoartemisinyl cyanophenylmethyl succinate ***(4a)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.46 (m, 5H, Ar–H); 6.40 (s, 1H, Ha); 5.76 (d, 1H, 12-H, [$J = 9.92$ Hz]); 5.42 (s, 1H, 5-H); 2.75 (m, 4H, –$COCH_2CH_2CO$–); 1.46 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.79$ Hz]); 0.83 (d, 3H, 10-CH_3, [$J = 7.10$ Hz]).

IR (KBr, cm^{-1}): 1753.0, 1452.2, 1151.3.

5.1.1.7. 12α-Deoxoartemisinyl cyano-2′-chlorophenylmethyl succinate ***(4b)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.70 (m, 1H, Ar–H); 7.41 (m, 3H, Ar–H); 6.70 (s, 1H, Ha); 5.77 (d, 1H, 12-H, [$J = 9.79$ Hz]); 5.41 (s, 1H, 5-H); 2.77 (m, 4H, –CO CH_2CH_2CO–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.91$ Hz]); 0.82 (d, 3H, 10-CH_3, [$J = 7.06$ Hz]).

IR (KBr, cm^{-1}): 1754.9, 1363.4, 1141.7, 1101.2, 1016.3.

5.1.1.8. 12α-Deoxoartemisinyl cyano-4′-chlorophenylmethyl succinate ***(4c)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.43 (m, 4H, Ar–H); 6.38 (s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.70$ Hz]); 5.41 (s, 1H, 5-H); 2.74 (m, 4H, –CO CH_2CH_2CO–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.85$ Hz]); 0, 79 (d, 3H, l5-CH_3, [$J = 7.12$ Hz]).

IR (KBr, cm^{-1}): 1754.9, 1494.6, 1143.6, 1097.3, 1016.3.

5.1.1.9. 12α-Deoxoartemisinyl cyano-2′-bromophenylmethyl succinate ***(4d)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.71 (d, 1H, Ar–H, [$J =$ 7.70 Hz]); 7.62 (d, 1H, Ar–H, [$J = 7.90$ Hz]); 7.43 (t, 1H, Ar–H); 7.32 (t, 1H, Ar–H); 6.71, 6.67 (s, s, 1H, Ha); 5.76 (d, 1H, 12-H, [$J = 9.90$ Hz]); 5.41 (s, 1H, 5-H); 2.79 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 6.03$ Hz]); 0.83 (d, 3H, 10-CH_3, [$J = 7.30$ Hz]).

IR (KBr, cm^{-1}): 1754.9, 1141.7, 1016.3.

5.1.1.10. 12α-Deoxoartemisinyl cyano-4′-bromophenylmethyl succinate ***(4e)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.58 (d, 2H, Ar–H, [$J =$ 8.43 Hz]); 7.38 (d, 2H, Ar–H, [$J = 8.39$ Hz]); 6.37 (s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.72$ Hz]); 5.49 (s, 1H, 5-H); 2.74 (m, 4H, –CO CH_2CH_2CO–); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.72$ Hz]); 0.82, 0.77 (d, d, 3H, 10-CH_3, [$J = 7.08$, 7.16 Hz]).

IR (KBr, cm^{-1}): 1754.9, 1494.6, 1143.6, 1097.3, 1016.3.

5.1.1.11. 12α-Deoxoartemisinyl cyano-4′-cyano-phenylmethyl succinate ***(4f)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.75 (m, 2H, Ar–H); 7.65 (m, 2H, Ar–H); 6.47 (s, 1H, Ha); 5.73 (d, 1H, 12-H, [$J = 8.92$ Hz]); 5.41 (s, 1H, 5-H); 2.77 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.68$ Hz]); 0.80 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 2231.3, 1754.9, 1141.7, 1016.3.

5.1.1.12. 12α-Deoxoartemisinyl cyano-4′-nitro-phenylmethyl succinate ***(4g)***

^{1}H NMR ($CDCl_3$, δ ppm): 8.31 (m, 2H, Ar–H); 7.72 (m, 2H, Ar–H); 6.52 (s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.84$ Hz]); 5.41 (s, 1H, 5-H); 2.76 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 6.67$ Hz]); 0.83 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 1753.0, 1702.9, 1658.5, 1600.7, 1209.2, 1132.2, 1016.3.

5.1.1.13. 12α-Deoxoartemisinyl cyano-4′-methoxy-phenylmethyl succinate ***(4h)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.42 (m, 2H, Ar–H); 6.92 (m, 2H, Ar–H); 6.34, 6.33 (s, s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.84$ Hz]); 5.40 (s, 1H, 5-H); 2.72 (m, 4H, –$COCH_2CH_2CO$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.83$ Hz]); 0.82 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 1751.1, 1612.2, 1132.2, 1016.3.

5.1.1.14. 12α-Deoxoartemisinyl cyano-2′,4′-dimethoxy-phenylmethyl succinate ***(4i)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.45 (d, 1H, Ar–H, [$J = 8.47$ Hz]); 6.61 (s, 1H, Ar–H); 6.52 (d, 1H, Ar–H, [$J = 8.51$ Hz]); 6.45 (s, 1H, Ha); 5.75 (d, 1H, 12-H, [$J = 9.86$ Hz]); 5.41 (s, 1H, 5-H); 3.82, 3.81 (s, s, 6H, Ar–OCH_3); 2.74 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.68$ Hz]); 0.81 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 1751.1, 1702.9, 1616.1, 1510.0, 1211.1, 1143.2, 1016.3.

5.1.1.15. 12α-Deoxoartemisinyl cyano-3′,4′-dimethoxy-phenylmethyl succinate ***(4j)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.07 (d, 1H, Ar–H, [$J = 8.37$ Hz]); 6.97 (s, 1H, Ar–H); 6.87 (d, 1H, Ar–H, [$J = 8.36$ Hz]); 6.36, 6.35 (s, s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.91$ Hz]); 5.39 (s, 1H, 5-H); 3.90, 3.88 (s, s, 6H, Ar–OCH_3); 2.74 (m, 4H, –$COCH_2CH_2CO$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.96$ Hz]); 0.82, 0.77 (d, d, 3H, 10-CH_3, [$J = 7.10$, 7.12 Hz]).

IR (KBr, cm^{-1}): 2117.5, 1751.1, 1519.7, 1259.3, 1143.6, 1018.2.

5.1.1.16. 12α-Deoxoartemisinyl cyano-3′-methoxy-4′-benzyloxyphenylmethyl succinate ***(4k)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.35 (m, 5H, Ar–H); 6.99 (m, 2H, Ar–H); 6.88 (m, 1H, Ar–H); 6.35, 6.33 (s, s, 1H, Ha); 5.74 (d, 1H, 12-H, [$J = 9.90$ Hz]); 5.40 (s, 1H, 5-H); 5.16 (s, 2H, Ar–CH_2); 3.91 (s, 3H, Ar–OCH_3); 2.71 (m, 4H, –$COCH_2CH_2CO$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.79$ Hz]); 0.79 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 1751.1, 1702.9, 1616.1, 1510.0, 1211.1, 1143.2, 1016.3.

5.1.1.17. 12α-Deoxoartemisinyl cyano-3′,4′-methylenedioxyphenylmethyl succinate ***(4l)***

^{1}H NMR ($CDCl_3$, δ ppm): 6.98 (d, 1H, Ar–H, [$J = 7.98$ Hz]); 6.96 (s, 1H, Ar–H); 6.82 (d, 1H, Ar–H, [$J = 7.95$ Hz]); 6.30 (s, 1H, Ha); 6.00 (s, 2H, –OCH_2O–); 5.75 (d, 1H, 12-H, [$J = 9.97$ Hz]); 5.41 (s, 1H, 5-H); 2.73 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 6.05$ Hz]); 0.81 (m, 3H, 10-CH_3).

IR (KBr, cm^{-1}): 1751.1, 1490.7, 1448.3, 1249.7, 1143.6, 1037.5, 1016.3.

5.1.1.18. 12α-Deoxoartemisinyl cyano-2′-chlorophenylmethyl adipate ***(4m)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.70 (m, 1H, Ar–H); 7.40 (m, 3H, Ar–H); 6.69 (1H, s, Ha); 5.76 (d, 1H, 12-H, [$J = 9.89$ Hz]); 5.41 (s, 1H, 5-H); 2.38 (m, 4H, –$COCH_2$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.86$ Hz]); 0.82 (d, 3H, 10-CH_3, [$J = 7.14$ Hz]).

IR (cm^{-1}): 1751.1, 1490.7, 1376.9, 1143.6, 1012.5, 875.5, 825.4.

5.1.1.19. 12α-Deoxoartemisinyl cyanophenylmethylpimelate ***(4n)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.48 (m, 5H, Ar–H); 6.40 (1H, s, Ha); 5.75 (d, 1H, 12-H, [$J = 9.90$ Hz]); 5.41 (s, 1H, 5-H); 2.71 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.91$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.11$ Hz]).

IR (cm^{-1}): 1751.1, 1490.7, 1376.9, 1143.6, 1012.5, 875.5, 825.4.

5.1.1.20. 12α-Deoxoartemisinyl cyano-2′-bromophenylmethyl azelaate ***(4o)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.71 (d, 1H, Ar–H, [$J = 7.71$ Hz]); 7.62 (d, 1H, Ar–H, [$J = 7.83$ Hz]); 7.43 (t, 1H, Ar–H); 7.32 (t, 1H, Ar–H); 6.65 (s, 1H, Ha); 5.77 (d, 1H, 12-H, [$J = 9.79$ Hz]); 5.42 (s, 1H, 5-H); 2.71 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.70$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.11$ Hz]).

IR (cm^{-1}): 1751.1, 1490.7, 1376.9, 1143.6, 1012.5, 875.5, 825.4.

*5.1.1.21. Succinic acid 12α-deoxoartemisinyl ester cyanophenylmethyl amide (**5a**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.45 (m, 2H, Ar–H); 7.40 (m, 3H, Ar–H); 6.58 (br d, 1H, N–H, [$J = 8.18$ Hz]); 6.11, 6.07 (d, d, 1H, Ha, [$J = 8.20$ Hz]); 5.74, 5.70 (d, d, 1H, 12-H, [$J = 9.75$, 9.74 Hz]); 5.38, 5.28 (s, s, 1H, 5-H); 2.74 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, -$COCH_2$–); 1.39, 1.38 (s, s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.02$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 6.96$ Hz]).

IR (KBr, cm^{-1}): 3374.9, 1764.6, 1697.1, 1510.0, 1159.0, 1018.2.

*5.1.1.22. Succinic acid 12α-deoxoartemisinyl ester cyano-2′-fluorophenylmethyl amide (**5b**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.48 (t, 1H, Ar–H); 7.35 (m, 1H, Ar–H); 7.19 (m, 1H, Ar–H); 7.10 (m, 1H, Ar–H); 6.60, 6.52 (d, d, 1H, N–H, [$J = 8.25$, 8.26 Hz]); 6.13 (d, 1H, Ha, [$J = 8.24$ Hz]); 5.70, 5.66 (d, 1H, 12-H, [$J = 9.89$, 9.91 Hz]); 5.34, 5.31 (s, s, 1H, 5-H); 2.70 (m, 2H, –$COCH_2$–); 2.47 (m, 2H, –$COCH_2$–); 1.33 (s, 3H, 4-CH_3); 0.89 (d, 3H, 11-CH_3, [$J = 6.05$ Hz]); 0.76, 0.74 (d, d, 3H, 10-CH_3, [$J = 7.14$, 7.14 Hz]).

IR (KBr, cm^{-1}): 3249.5, 1751.1, 1646.9, 1529.3, 1170.6, 1039.5, 1018.2.

*5.1.1.23. Succinic acid 12α-deoxoartemisinyl ester cyano-3′-fluorophenylmethyl amide (**5c**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.39 (m, 1H, Ar–H); 7.27 (d, 1H, Ar–H, [$J = 6.09$ Hz]); 7.19 (d, 1H, Ar–H, [$J =$ 9.19 Hz]); 7.09 (t, 1H, Ar–H); 6.62 (br d, [$J = 8.40$ Hz], 1H, N–H); 6.16 (d, [$J = 8.48$ Hz], 1H, Ha); 5.71 (d, [$J = 9.88$ Hz], 1H, 12-H); 5.29 (s, 1H, 5-H), 2.83 (m, 2H, –$COCH_2$–); 2.59 (m, 2H, –$COCH_2$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.30$ Hz]); 0.82 (d, 3H, 10-CH_3, [$J = 7.04$ Hz]).

IR (KBr, cm^{-1}): 3361.4, 1729.9, 1666.2, 1500.4, 1164.8, 1018.2.

*5.1.1.24. Succinic acid 12α-deoxoartemisinyl ester cyano-4′-fluorophenylmethyl amide (**5d**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.46 (m, 2H, Ar–H); 7.09 (m, 2H, Ar–H); 6.72 (br d, 1H, NH, [$J = 8.20$ Hz]); 6.10, 6.06 (d, d, 1H, Ha, [$J = 8.22$ Hz]); 5.73, 5.68 (d, d, 1H, 12-H, [$J = 9.79$, 9.81 Hz]); 5.37, 5.28 (s, s, 1H, 5-H), 2.80 (m, 2H, –$COCH_2$–); 2.50 (m, 2H, –$COCH_2$–); 1.38 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.09$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.00$ Hz]).

IR (KBr, cm^{-1}): 3365.2, 1731.8, 1670.1, 1510.0, 1161.0, 1161.0, 1018.2.

*5.1.1.25. Succinic acid 12α-deoxoartemisinyl ester cyano-3′-chlorophenylmethyl amide (**5e**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.48 (s, 1H, Ar–H); 7.36 (m, 3H, Ar–H); 6.83 (br, 1H, N–H); 6.15, 6.09 (d, d, 1H, Ha, [$J = 8.41$, 8.38 Hz]); 5.75, 5.70 (d, d, 1H, 12-H, [$J = 9.80$, 9.79 Hz]); 5.38, 5.25 (s, s, 1H, 5-H); 2.76 (m, 2H, –$COCH_2$–); 2.54 (m, 2H, –$COCH_2$–); 1.39, 1.37 (s, s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.30$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.01$ Hz]).

IR (KBr, cm^{-1}): 3370.0, 3334.4, 2250.6, 1762.6, 1731.8, 1695.1, 1670.1, 1376.9, 1161.0, 1016.3.

*5.1.1.26. Succinic acid 12α-deoxoartemisinyl ester cyano-4′-chlorophenylmethyl amide (**5f**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.40 (m, 4H, Ar–H); 6.73 (br d, 1H, N–H, [$J = 8.24$ Hz]); 6.12, 6.08 (d, d, 1H, Ha, [$J = 8.25$, 8.28 Hz]); 5.73, 5.67 (d, d, 1H, 12-H, [$J = 9.76$, 9.79 Hz]); 5.38, 5.23 (s, s, 1H, 5-H); 2.74 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, –$COCH_2$–); 1.38 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.39$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 6.97$ Hz]).

IR (KBr, cm^{-1}): 3332.4, 1764.6, 1693.2, 1515.8, 1157.1, 1016.3.

*5.1.1.27. Succinic acid 12α-deoxoartemisinyl ester cyano-2′-bromophenylmethyl amide (**5g**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.67 (d, 1H, Ar–H, [$J =$ 6.56 Hz]); 7.62 (d, 1H, Ar–H, [$J = 7.82$ Hz]); 7.41 (t, 1H, Ar–H); 7.28 (t, 1H, Ar–H); 6.56 (br d, 1H, N–H, [$J = 7.43$ Hz]); 6.22 (d, 1H, Ha, [$J = 7.42$ Hz]); 5.74 (d, 1H, 12-H, [$J = 9.88$ Hz]); 5.39 (s, 1H, 5-H); 2.77 (m, 2H, –$COCH_2$–); 2.56 (m, 2H, –$COCH_2$–); 1.40 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.86$ Hz]); 0.82 (d, 3H, 10-CH_3, [$J = 7.01$ Hz]).

IR (cm^{-1}): 3228.3, 1753.0, 1646.9, 1531.2, 1151.3, 1041.4, 1016.3.

*5.1.1.28. Succinic acid l2α-deoxoartemisinyl ester cyano-3′-bromophenylmethyl amide (**5h**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.63, 7.62 (s, s, 1H, Ar–H); 7.51 (d, 1H, Ar–H, [$J = 7.63$ Hz]); 7.41 (d, 1H, Ar–H, [$J = 7.57$ Hz]); 7.29 (t, 1H, Ar–H); 6.85, 6.81 (d, d, 1H, N–H, [$J = 8.45$, 8.43 Hz]); 6.14, 6.08 (d, d, 1H, Ha, [$J = 8.47$, 8.45 Hz]); 5.74, 5.69 (d, d, 1H, 12-H, [$J = 9.90$, 9.88 Hz]); 5.37, 5.22 (s, s, 1H, 5-H); 2.74 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, –$COCH_2$–); 1.38, 1.37 (s, s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 4.88$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J = 7.02$ Hz]).

IR (KBr, cm^{-1}): 3372.9, 3338.2, 2250.6, 1760.7, 1731.8, 1697.1, 1670.1, 1376.9, 1161.0, 1029.8.

*5.1.1.29. Succinic acid 12α-deoxoartemisinyl ester cyano-4′-bromophenylmethyl amide (**5i**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.55, 7.53 (d, d, 2H, Ar–H, [$J = 8.22$, 8.20 Hz]); 7.38, (d, 2H, Ar–H, [$J = 8.21$ Hz]); 6.81 (br d, 1H, N–H); 6.11, 6.06 (d, d, 1H, Ha, [$J = 8.41$, 8.39 Hz]); 5.73, 5.66 (d, d, 1H, 12-H, [$J = 9.76$, 9.77 Hz]); 5.37, 5.19 (s, s, 1H, 5-H); 2.74 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, –$COCH_2$–); 1.38 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.70$ Hz]); 0.81 (d, 3H, 10-CH_3, [$J =$ 7.05 Hz]).

IR (KBr, cm^{-1}): 3357.5, 1764.6, 1731.8, 1696.2, 1664.3, 1159.0, 1016.3.

*5.1.1.30. Succinic acid 12α-deoxoartemisinyl ester cyano-4′-N,N-dimethylphenylmethyl amide (**5j**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.30 (d, 4H, Ar–H, [$J =$ 8.53 Hz]); 6.72 (br, 1H, N–H); 6.29 (d, 1H, Ha, [$J = 7.28$ Hz]); 5.92, 5.78 (d, d, 1H, 12-H, [$J = 9.80$, 9.79 Hz]); 5.40 (s, 1H, 5-H); 2.97 (s, 6H, NMe_2); 2.78 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, –$COCH_2$–); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.60$ Hz]); 0.84 (d, 3H, 10-CH_3, [$J = 7.08$ Hz]).

IR (KBr, cm^{-1}): 3365.2, 2242.8, 1731.8, 1666.2, 1525.4, 1161.0, 1027.9.

*5.1.1.31. Succinic acid 12α-deoxoartemisinyl ester cyano-2′-naphylmethyl amide (**5k**)*

^{1}H NMR ($CDCl_3$, δ ppm): 8.03, 8.01 (s, s, 1H, Ar–H); 7.88 (m, 2H, Ar–H); 7.82 (m, 1H, Ar–H); 7.50 (m, 3H, Ar–H); 6.86, 6.68 (d, d, 1H, N–H, [$J = 8.38$, 8.34 Hz]); 6.32, 6.26 (d, d, 1H, Ha, [$J = 8.38$, 8.35 Hz]); 5.72, 5.59 (d, d, 1H, 12-H, [$J = 9.96$, 9.92 Hz]); 5.26, 4.78 (s, s, 1H, 5-H); 2.78 (m, 2H, –$COCH_2$–); 2.55 (m, 2H, –$COCH_2$–); 1.39, 1.37 (s, s, 3H, 4-CH_3); 0.83 (d, 3H, 11-CH_3, [$J = 5.30$ Hz]); 0.76 (d, 3H, 10-CH_3, [$J = 7.05$ Hz]).

IR (KBr, cm^{-1}): 3363.3, 2244.8, 1731.6, 1666.2, 1508.1, 1162.9, 1027.9.

*5.1.1.32. Preparation of compound **7***

The solution of *N*-methyl-α-aminoarylacetonitrile (12 mmol), cyclic anhydride (10 mmol) and 1 mL triethylamine in 50 mL CH_2Cl_2 was stirred at r.t. for 4 h. After the completion of the reaction the solution was washed by 5% HCl, saturated brine, and dried over $MgSO_4$ successively. The solvent was evaporated under reduced pressure. The residue, compound **7**, could be used for the next procedure without further purification.

*5.1.1.33. Succinic acid mono-N-methycyano-4′-bromophenylmethyl amide (**7h**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.53 (d, 2H, Ar–H, [$J =$ 8.36 Hz]); 7.27 (d, 2H, Ar–H, [$J = 8.35$ Hz]); 7.02 (s, 1H, Ha); 2.91 (s, 3H, N–CH_3); 2.70 (m, 4H, –$COCH_2CH_2CO$–).

IR (cm^{-1}): 3050 (w); 1716.4; 1646.9; 1488.8; 1400.1; 1253.5; 1226.5; 1010.5.

*5.1.1.34. Preparation of compound **6***

Compound **6** was prepared by the condensation of compound **7** with dihydroartemisinin (**1b**) as in the preparation of compound **4**.

*5.1.1.35. Succinic acid 12α-deoxoartemisinyl ester N-methylcyanophenylmethyl amide (**6a**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.39 (s, 5H, Ar–H); 7.07 (s, 1H, Ha); 5.79 (d, 1H, 12-H, [$J = 9.71$ Hz]); 5.43 (s, 1H, 5-H); 2.90 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.42 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.73$ Hz]); 0.87 (d, 3H, 10-CH_3, [$J = 7.03$ Hz]).

IR (KBr, cm^{-1}): 2242.8, 1747.2, 1656.6, 1407.8, 1170.6, 1016.3.

*5.1.1.36. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-2′-fluorophenylmethyl amide (**6b**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.59 (t, 1H, Ar–H); 7.39 (d, 1H, Ar–H, [$J = 6.58$ Hz]); 7.21 (d, 1H, Ar–H, [$J =$ 7.42 Hz]); 7.10 (t, 1H, Ar–H); 7.10 (s, 1H, Ha); 5.79, 5.77 (d, d, 12-H, [$J = 9.72$, 9.70 Hz]); 5.42 (s, 1H, 5-H); 2.93 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4–CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.86$ Hz]); 0.85 (d, 3H, 10-CH_3, [$J = 7.04$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1751.1, 1666.2, 1492.7, 1164.8, 1101.2, 1018.2.

*5.1.1.37. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-3′-fluorophenylmethyl amide (**6c**)*

^{1}H NMR ($CDCl_3$, δ ppm): 7.40 (m, 2H, Ar–H); 7.21, 7.19 (s, s, 1H, Ar–H); 7.08 (t, 1H, Ar–H); 7.06, 7.04 (s, s, 1H, Ha); 5.80, 5.79 (d, d, 12-H, [$J = 9.76$, 9.80 Hz]); 5.43 (s, 1H, 5-H); 2.93 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.67$ Hz]); 0.86 (d, 3H, 10-CH_3, [$J = 6.86$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1751.1, 1446.4, 1164.8, 1016.3.

5.1.1.38. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-4′-fluorophenylmethyl amide ***(6d)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.38 (m, 2H, Ar–H); 7.09 (m, 2H, Ar–H); 7.04 (s, 1H, Ha); 5.78 (d, 12-H, [$J = 9.72$ Hz]); 5.43 (s, 1H, 5-H); 2.90 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.42 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.54$ Hz]); 0.86 (d, 3H, 10-CH_3, [$J = 6.93$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1747.2, 1654.7, 1510.0, 1016.3.

5.1.1.39. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-2′-chlorophenylmethyl amide ***(6e)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.73 (t, 1H, Ar–H); 7.39 (m, 3H, Ar–H); 7.03 (s, 1H, Ha); 5.78 (d, 12-H, [$J = 9.89$ Hz]); 5.42 (s, 1H, 5-H); 2.81 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.75$ Hz]); 0.85 (d, 3H, 10-CH_3, [$J = 7.07$ Hz]).

IR (KBr, cm^{-1}): 1747.2, 1662.4, 1170.6, 1099.2, 1012.5.

5.1.1.40. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-4′-chlorophenylmethyl amide ***(6f)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.38 (d, 2H, Ar–H, [$J = 8.25$ Hz]); 7.33 (d, 2H, Ar–H, [$J = 8.27$ Hz]); 7.04 (s, 1H, Ha); 5.78 (d, 12-H, [$J = 9.58$ Hz]); 5.43 (s, 1H, 5-H); 2.90 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.56$ Hz]); 0.86 (d, 3H, 10-CH_3, [$J = 6.87$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1747.2, 1654.7, 1492.7, 1407.8, 1099.2, 1016.3.

5.1.1.41. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-2′-bromophenylmethyl amide ***(6g)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.75 (d, 1H, Ar–H, [$J = 7.78$ Hz]); 7.62 (d, 1H, Ar–H, [$J = 7.80$ Hz]); 7.42 (t, 1H, Ar–H); 7.29 (t, 1H, Ar–H); 6.91, 6.90 (s, 5, 1H, Ha); 5.79, 5.77 (d, d, 12-H, [$J = 9.80$, 9.77 Hz]); 5.42 (s, 1H, 5-H); 2.82, 2.79 (s, s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.86$ Hz]); 0.85 (d, 3H, 10-CH_3, [$J = 6.98$ Hz]).

IR (KBr, cm^{-1}): 1751.1, 1666.2, 1471.4, 1376.9, 1018.2.

5.1.1.42. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-4′-bromophenylmethyl amide ***(6h)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.54 (d, 2H, Ar–H, [$J = 8.34$ Hz]); 7.27 (d, 2H, Ar–H, [$J = 8.33$ Hz]); 7.02, 7.01 (s, s, 1H, Ha); 5.80, 5.78 (d, d, 1H, 12-H, [$J = 9.79$, 9.80 Hz]); 5.43 (s, 1H, 5-H); 2.92, 2.90 (s, s, 3H, N–CH_3); 2.75 (m, 4H, –$COCH_2CH_2CO$–); 1.42 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.72$ Hz]); 0.86 (d, 3H, 10-CH_3, [$J = 7.14$ Hz]).

IR (cm^{-1}): 2244.8, 1749.1, 1662.4, 1488.8, 1403.9, 1164.8, 1012.5, 877.5.

5.1.1.43. Succinic acid 12α-deoxoartemisinyl ester N-methylcyano-2′,3′-dimethyiphenylmethyl amide ***(6i)***

^{1}H NMR ($CDC1_3$, δ ppm): 7.52 (d, 1H, Ar–H, [$J = 7.73$ Hz]); 7.07 (d, 1H, Ar–H, [$J = 7.70$ Hz]); 7.01 (s, 1H, Ar–H); 6.93 (s, 1H, Ha); 5.79, 5.77 (d, d, 12-H, [$J = 9.30$, 9.28 Hz]); 5.42 (s, 1H, 5-H); 2.83, 2.81 (s, s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 2.31 (s, 3H, Ar–CH_3); 2.11, 2.09 (s, s, 3H, Ar–CH_3); 1.41 (s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.73$ Hz]); 0.86 (d, 3H, 10-CH_3, [$J = 6.87$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1751.1, 1662.4, 1164.8, 1016.3.

5.1.1.44. Succinic acid 12α-deoxoartemtsinyl ester N-methylcyano-3′-(3-trifluoromethylphenyl)-phenylmethyl amide ***(6j)***

^{1}H NMR ($CDCl_3$, δ ppm): 7.47–7.36 (m, 3H, Ar–H); 7.21, 7.19 (s, s, 2H, Ar–H); 7.15–7.06 (m, 3H, Ar–H); 6.98, 6.97 (s, s, 1H, Ha); 5.79, 5.76 (d, d, 12-H, [$J = 10.02$, 10.00 Hz]); 5.42, 5.41 (s, s, 1H, 5-H); 2.94 (s, 3H, N–CH_3); 2.80 (m, 4H, –$COCH_2CH_2CO$–); 1.41 (s, 3H, 4-CH_3); 0.94 (d, 3H, 11-CH_3, [$J = 5.12$ Hz]); 0.84 (d, 3H, 10-CH_3, [$J = 7.01$ Hz]).

IR (KBr, cm^{-1}): 2244.8, 1751.1, 1662.4, 1450.2, 1328.7, 1166.7, 1130.1, 1018.2.

5.1.1.45. Phthalic acid 12α-deoxoartemisinyl ester N-methylcyanophenylmethyl amide ***(6k)***

^{1}H NMR ($CDCl_3$, δ ppm): 8.21 (d, 1H, Ar–H, [$J = 7.98$ Hz]); 7.63–7.29 (m, 8H, Ar–H); 7.23 (s, 1H, Ha); 6.02 (d, 1H, 12-H, [$J = 9.72$ Hz]); 5.50, 5.47 (s, s, 1H, 5-H); 2.63, 2.62 (s, 3H, N–CH_3); 1.42, 1.39 (s, s, 3H, 4-CH_3); 0.97 (d, 3H, 11-CH_3, [$J = 6.00$ Hz]); 0.84 (d, 3H, 10-CH_3, [$J = 7.07$ Hz]).

IR (KBr, cm^{-1}): 1733.7, 1658.5, 1384.7, 1263.2, 1033.7, 1016.3.

5.1.1.46. Maleic acid 12α-deoxoartemisinyl ester N-methylcyanophenylmethyl amide ***(6l)***

^{1}H NMR ($CDCI_3$, δ ppm): 7.57 (d, 1H, Ar–H, [$J = 7.17$ Hz]); 7.52 (d, 1H, Ar–H, [$J = 7.14$ Hz]); 7.43 (m,

3H, Ar–H); 7.07, 7.06 (s, s, 1H, Ha); 6.60, 6.57 (d, d, 1H, =C–H, [$J = 9.45$, 9.41 Hz]); 6.20, 6.17 (s, s, 111, 5-H); 5.85, 5.82 (d, d, 1H, =C–H, [$J = 10.22$, 10, 27 Hz]); 5.44 (d, 1H, 12-H, [$J = 6.18$ Hz]); 2.83 (s, 3H, N–CH_3); 1.41, 1.39 (s, s, 3H, 4-CH_3); 0.95 (d, 3H, 11-CH_3, [$J = 5.87$ Hz]); 0.85, 0.81 (d, d, 3H, 10-CH_3, [$J = 7.08$, 7.10 Hz]).

IR (KBr, cm^{-1}): 1735.6, 1658.5, 1452.2, 1405.9, 1207.2, 1016.3.

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